Paul Davis

Gold Therapy in the Treatment of Rheumatoid Arthritis

SUMMARY

For many years, gold therapy has been the mainstay in the management of patients with progressive rheumatoid disease. At the present time two forms of gold therapy are available: one by injection and the other by the oral route. A significant number of patients will achieve clinical benefit from treatment with one of these two compounds. Both compounds have a high prevalence of side-effects and should be regarded as toxic, although the oral preparation appears to have a somewhat better safety profile than has the injectable compound. While resort to these medications should be considered for the treatment of patients who have progressive rheumatoid disease, their use should not be taken lightly. The prescribing physician has an obligation to ensure constant monitoring of patients who are receiving either of these therapies. (*Can Fam Physician* 1988; 34:445–452.)

Key words: gold therapy, rheumatoid arthritis

RÉSUMÉ

Les sels d'or constituent depuis longtemps le pivot du traitement des patients souffrant d'une polyarthrite rhumatoïde évolutive. Les sels d'or sont offerts sous deux formes: injectable et orale. Un nombre appréciable de patients obtiendront des bienfaits cliniques de l'une ou l'autre forme de traitement. Les deux composés comportent un risque élevé d'effets secondaires et devraient être considérés comme étant toxiques, même si la préparation orale semble offrir un profil plus sécuritaire que le composé injectable. Bien qu'on puisse envisager prescrire ces médicaments pour le traitement des patients présentant une arthrite rhumatoïde évolutive, il ne faut pas les utiliser à la légère. Le médecin qui les prescrit a le devoir d'exercer une surveillance étroite des patients recevant l'une ou l'autre forme de traitement.

Dr. Davis is professor of Medicine, Division of Rheumatology, in the Department of Medicine of the University of Alberta. Requests for reprints to: 9-112 Clinical Sciences Building, University of Alberta, Edmonton, Alta. T6G 2G3

IN 1927, LANDE REPORTED the use of aurothioglucose, by injection, in patients with a variety of rheumatic diseases, on the misconception that these conditions were caused by infectious agents.[1] This observation was taken up by Forestier who, acting on the same supposition, first reported the use of this compound in the treatment of patients with rheumatoid arthritis.[2] Forestier's initial observations were encouraging and led, over the next few years, to further reports on the use of this treatment by himself and other investigators. Despite the therapeutic benefit observed, concern was expressed about the high prevalence of potentially serious side-effects experienced by patients on this medication. Numerous uncontrolled studies were performed during the 1930s and early 1940s, but the first double-blind controlled study, undertaken by Fraser,[3] was not reported till 1945. It was not until the controlled study of the Empire Rheumatism Council, reported in 1960 and 1961, that gold therapy was more widely regarded as an appropriate and effective therapy for rheumatoid disease.[4, 5] In all the studies carried out over these four decades, however, the problem of toxicity remained paramount. In the United States, the 1973 report of the Cooperating Clinics generally supported the conclusions of previous studies.[6] Because of its potential benefit, gold therapy has remained one of the key disease-modifying anti-rheumatic drugs in the management of patients with progressive rheumatoid disease. In the last few years a new dimension has been added to the use of gold therapy in the treatment of rheumatoid arthritis by the development of an oral gold preparation, Auranofin.[7] Both the injectable and the oral form of gold medication remain effective therapeutic agents in the management of patients with rheumatoid disease, even though the problem of potential and sometimes significant toxicity remains largely unsolved.

Choice of Gold Therapy in Treating Rheumatoid Disease

Although there are no definitive objective criteria on which a physician can base decisions to use a particular disease-modifying anti-rheumatic drug, some general guidelines are widely used by rheumatologists. These decisions are principally empirical and based on experience garnered from

clinical observations. In general, gold therapy is reserved for those patients with established rheumatoid disease who, despite the use of more conventional therapy such as non-steroidal anti-inflammatory medications, analgesics, and physiotherapy, have failed to show signficant improvement in their active synovitis, or in whom the disease is progressing. Most physicians would observe patients over a three- to six-month period to establish a diagnosis and the nature of the disease's progression before deciding to use gold therapy.

For some patients, however, the decision should be made earlier, as there is evidence to suggest that the earlier gold therapy is started in the course of the disease, the more effective it may be. When, for instance, patients present with established rheumatoid disease associated with erosive change already obvious on radiographs, high titres of rheumatoid factor, or extra-articular manifestations such as rheumatoid nodules and vasculitis, gold therapy should be started immediately, as it is unlikely that more conventional therapy will influence the disease process.

In addition to its use in treating rheumatoid disease, gold therapy may also be indicated for certain subsets of patients suffering from juvenile chronic polyarthritis, palindromic rheumatism, psoriatic arthritis, and ankylosing spondylitis. At the present time one form or other of gold therapy is generally regarded as being the treatment of choice in patients with progressive disease who have not responded to initial therapy with other medication. In comparative clinical studies that compared the use of gold therapy with that of penicillamine, chloroquine and immunosuppresive agents, it has been found that gold therapy compared very favourably with the other medications, both clinically and in regard to toxicity.[8-10] Once a patient has been started on gold therapy, most physicians would continue the drug indefinitely, although long-term studies have clearly demonstrated that with time, the number of patients who will be able to continue on this therapy drops considerably, either because it fails to control the disease process, or because the patient develops a significant toxic reaction.[11] Fortunately, in those patients who respond well to the therapy, and who do not develop significant toxicity, there are very few contraindications to the continued use of gold therapy. In fact, gold therapy has not been shown to cause any significant drug interactions, and despite accumulation of the medication in the tissues, it has not been shown to cause any significant permanent tissue damage.

Toxicity

The major problem associated with gold therapy is the high prevalence of toxic reactions observed though figures vary considerably from study to study. Although some studies have reported a toxic reaction in up to 35% of cases, greater understanding of the etiology of such reactions has resulted in substantially more patients being able to tolerate therapy. The development of the new oral gold preparation Auranofin seems to offer an alternative form of therapy with a toxicity profile that is potentially less serious than that observed with the injectable form of gold medication.[12]

Mucocutaneous reactions occur with all gold compounds, although their prevalence is somewhat less in patients treated with the oral gold preparation. Very rarely do these reactions necessitate the discontinuance of gold therapy. A variety of skin conditions have been described in association with gold compounds, although the only significant — and fortunately rare — side-effect is that of exfoliative dermatitis. Aphthous ulceration and stomatitis are both seen, but clinical experience suggests that these reactions can usually be managed satisfactorily by temporary discontinuance or adjustment of dosage and frequency of therapy, depending on clinical outcome. In most cases, these reactions are of short duration, and many patients are able to continue their therapy despite annoying but non-threatening symptoms. When the more persistent or extensive mucocutaneous reactions occur they usually disappear rapidly, without causing permanent problems, on discontinuance of therapy, although their control occasionally requires the use of topical steroid therapy.[13, 14]

Gastrointestinal reactions to gold compounds are seen almost solely in those patients receiving the oral gold preparation. Mild upper GI symptoms do occur, but they are very rarely of any major clinical significance. A significant percentage of patients receiving the oral gold preparation suffer from loose bowels or frank diarrhea. This reaction, however, is often of little clinical importance; it usually occurs only at the beginning of therapy and is self limiting. Clinical studies have shown that this non-serious complication of oral gold therapy rarely requires discontinuation of the treatment, although if this step is necessary, the problem resolves rapidly without permanent sequellae.[15]

Nephrotoxicity is seen with the use of all gold compounds, although its prevalence is somewhat less with the use of the oral gold compound as compared to the injectable forms. Nephrotoxicity usually takes the form of mild proteinuria, although frank nephrotic syndrome is occasionally seen. When renal biopsies have been performed, they have demonstrated that this syndrome results from a membranous glomerular nephritis mediated by the deposition of immune complexes. Nephrotoxicity is very rarely a serious clinical problem and does not result in either acute or chronic renal failure. Once proteinuria has been detected, it is usually worthwhile to determine its extent by a 24-hour urine-protein analysis. In many centres, therapy is not stopped unless the reading exceeds 500 mg-1000 mg protein loss in 24 hours. In all cases alternative explanations for the proteinuria (e.g., urinary tract infections) should be excluded before the gold therapy is held responsible. Even if the proteinuria is of a severity sufficient to warrant discontinuance of treatment, it usually resolves spontaneously over a period of several months without evidence of permanent renal damage. Very occasionally, in more severe cases, the use of diuretics in association with a short course of systemic steroids may be indicated.[16, 17] In some circumstances, however, gold therapy has been continued in the presence of mild proteinuria without resulting in evidence of significant deterioration in renal function; and in some instances spontaneous resolution has occurred.

Hematologic reactions cause the greatest concern in the management of patients developing toxic reactions to gold therapy. It is important, however, to ensure that any hematologic reaction that a patient experiences during the course of gold therapy is indeed directly related to the therapy and is not the result of other causes or a manifestation of the disease itself, (e.g. Felty's syndrome).[18] The most common hematologic reaction experienced with all forms of gold therapy is eosinophilia. While this condition may

be seen in association with other reactions to gold therapy, particularly mucocutaneous side-effects, it is not regarded as a significant adverse reaction and is not an indicator of impending toxicity of any other sort.[19]

Thrombocytopenia is the most common of the more serious hematologic reactions that patients experience during a course of gold therapy. Again, this reaction occurs rather more often in patients receiving the injectable form of gold than in those receiving the oral form. Thrombocytopenia may occur either as a disease with characteristics similar to those of idiopathic thrombocytopenic purpura or as a manifestation of marrow suppression. The former type of thrombocytopenia usually occurs dramatically and unpredictably. The abnormality may be detected by routine screening, or the patient may report the development of purpura. Although it is a potentially serious side-effect to gold therapy, isoled thrombocytopenia without suppression of the white blood-cell count or an associated anemia usually responds completely and dramatically to discontinuance of gold therapy and the institution of systemic steroids. Unlike many of the other reactions to gold therapy, which usually occur early in the course of treatment, thrombocytopenia may occur at any time during the course of therapy, and the physician should always be on guard for its occurrence.[20] A patient's development of anti-platelet antibodies is sometimes a valuable aid in signalling impending gold-induced thrombocytopenia.

Isolated neutropenia has also been reported in association with gold therapy; again, alternative causes of the condition must be considered. Chronic, low-grade, intermittent neutropenia is generally regarded as of little consequence, although it is, of course, essential to ensure that this is not the forerunner of diffuse marrow hypoplasia as indicated by an associated fall in platelet count and the development of anemia. In patients with relatively mild intermittent neutropenia, gold therapy may be continued either on an unchanged regimen or at a reduced frequency or dosage.[21]

The most serious hematologic toxic reaction experienced with gold therapy is the development of aplastic anemia. This side-effect has so far been reported only with injectable gold medication and not as yet with the use of oral gold. Aplastic anemia usually occurs suddenly and unpredictably; the first sign is the development of thrombocytopenia, usually followed by the rapid development of both neutropenia and anemia. The development of this complication should be viewed as a medical emergency; it necessitates an immediate discontinuance of gold therapy and confirmation of the diagnosis by means of a bone-marrow biopsy. Immediate supportive measures are usually necessary, as this complication is associated with marked morbidity and mortality.[22]

Various miscellaneous reactions have been reported to the therapeutic use of gold compounds. The most common of these, seen almost exclusively with injectable gold, is the development of nitritoid reactions. Patients may complain of an increase in myalgia, arthralgia, a feeling of faintness, sweating, and, occasionally, shortness of breath. These post-injection reactions are usually mild and self-limiting, and tend to become milder with time, despite continuation of therapy. Very occasionally, patients' symptoms will be of sufficient severity to necessitate the discontinuance of treatment.[23] Various other abnormalities have been described in association with injectable gold, although at present there is too little evidence to suggest that the administration of the oral gold preparation will cause the same reactions. Gold lung,[24] cholestatic jaundice[25] and enterocolitis[26] have all been reported with injectable gold. Fortunately, all these reactions are extremely rare; when they do occur, however, therapy must be discontinued, and appropriate subspecialty consultation and management are usually required.

Monitoring and Management of Toxicity

Gold sodium thiomalate is a water-soluble compound that is administered intramuscularly at weekly intervals. It is usually advocated that test doses of 10 mg and 25 mg be given before initiating therapy with a dosage of 50 mg given intramuscularly at weekly intervals. There is, however, little evidence that the use of these test doses helps predict the subsequent development of a toxic reaction. Most physicians advocate the continued use of gold therapy 50 mg intramuscularly at weekly intervals until a total of 1 g of gold has been injected. This regimen is an empirical one based on clinical experience gained over the last 50 years. Some physicians, however, advocate an individual-based regimen of gold therapy with an injection frequency and dosage tailored to the requirements of individual patients, according to clinical outcome.[27] Once the patient has received a total of 1 g of gold, with subsequent therapeutic benefit, injections should be continued at a maintenance dosage, usually of 25 mg or 50 mg given intramuscularly every two to six weeks, depending on individual requirements. When patients receiving maintenance doses of gold show loss of disease control over time, an increase in the frequency or dosage of the medication often succeeds in bringing the disease under further control.

Auranofin is a lipophilic compound and has pharmacokinetic properties which allow it to cross the gastrointestinal mucosa. For this reason, this medication can be given orally. The recommended dosage is 3 mg b.i.d., although slightly lower or slightly higher doses can be tried in individual patients. However, the slightly higher dosage of 3 mg t.i.d. is associated with rather more adverse reactions.

Both these medications, as mentioned earlier, are associated with a significant number of adverse reactions, although reactions to Auranofin seem to occur somewhat less mildly and less frequently than do reactions to injectable gold. The manufacturers of both compounds recommend, however, that patients should be regularly screened for the development of toxicity. In most cases of mucocutaneous reaction, patients will report their symptoms directly to their physician, and no screening tests are of value for predicting the reaction. Screening tests are of value, however, in the assessment of hematologic reactions and nephrotoxicity. By contrast, thrombocytopenia and aplastic anemia may occur unpredictably and precipitously. Therefore the physician can not always rely on regular screening to give significant warning of the development of these potentially serious side-effects. If any doubt exists about the occurrence of either reaction, a bone-marrow examination should be performed immediately. Urinalysis should be performed routinely to look for aymptomatic proteinuria. Generally speaking, a trace or 1+ protein in the urine can be ignored, assuming that other explanations for its development have been excluded (e.g., urinary tract infection). However, if a patient develops increasing levels of proteinuria

on routine urinalysis or persistent low-grade proteinuria, it is usually advisable to arrange for a 24-hour urine protein to be obtained to quantify the protein loss more accurately. Opinion differs from centre to centre concerning the level of proteinuria at which the medication should be stopped, but in some cases use of gold compounds can be continued even in the presence of one gram of proteinuria over 24 hours.

There is still some debate in the literature on the optimal method of dealing with reactions occurring during the course of chrysotherapy. Certainly, with the more serious reactions, gold therapy must be discontinued. If thrombocytopenia occurs, systemic steroids are indicated, and their use usually brings about significant improvement. Similarly, nephrotoxicity may respond well to systemic steroids. The rare, but serious, complication of aplastic anemia obviously requires a good deal of supportive therapy. Various treatments have been advocated, including steroids, androgens, antilymphocyte globulin, and N-acetyl cysteine. At present there is very little evidence to suggest that any one of these substances is necessarily associated with hematologic improvement. In addition, there is little evidence to suggest that the use of the chelating agents, d-penicillamine or BAL, is of any benefit in the management of any toxic reactions seen in association with gold therapy.[28] Despite the high prevalence of side-effects reported in association with gold therapy, most of the side-effects are mild, and clinical common sense usually suggests the most appropriate form of management necessary beyond discontinuance of drug if, indeed, any additional form of therapy is necessary.

Comparative Benefits of Injectable and Oral Gold

Both forms of gold therapy have a use in the management of patients with progressive rheumatoid disease. Individual choice of therapy will depend on certain clinical criteria, although to date the literature is incomplete. Comparative studies suggest that injectable gold may be slightly more beneficial than oral gold in inducing disease remission. A larger number of patients receiving injections than of those receiving Auranofin are able to complete therapy. The drop-out rate resulting from insufficient therapeutic effect is somewhat higher for patients on Auranofin. In those patients who continue on the oral gold preparation, however, the quality of remission is similar to that obtained with injectable gold. By contrast, injectable gold is associated with a higher prevalence of side-effects and, in particular, a higher prevalence of the more serious side-effects such as nephrotoxicity, thrombocytopenia, and aplastic anemia.[29] Thus, a lower potential therapeutic benefit with the oral preparation offers an increased safety margin.

In family practice, Auranofin may prove to be a useful anti-rheumatic drug which can be satisfactorily used in a patient's management. Its oral route of administration and its lower toxicity profile allow for greater physician confidence, although its slightly reduced efficacy as compared to injectable gold must be taken into consideration. In addition, patient compliance must be addressed: only the informed and reliable patient should be prescribed an oral preparation of which the dose must not be exceeded, and of which the use requires monitoring. Auranofin, therefore, helps fill the gap between the NSAIDs and more potent disease-modifying drugs (injectable gold, d-Penicillamine, and Methotrexate), which up to now has been occupied only by the antimalarials. The decision to initiate Auranofin therapy in family practice should, however, be taken only when the diagnosis is well established and the physician is adequately informed about the drug's usage. Initiation of injectable gold in therapy is best reserved for patients who have had subspecialty consultation because of the drug's more serious potential toxicity. Day-to-day management and monitoring of injectable gold therapy remains a useful function of family practitioners with adequate subspecialist support. When initiating Auranofin therapy in family practice, however, it should be remembered that this therapy is significantly more costly than some alternatives, and cost may be a relevant factor to an economically stressed patient.[30]

Two recent Canadian studies have helped to determine the place for gold therapy in the treatment of rheumatoid arthritis. In the comparative study by Harth and colleagues,[31] the cumulative "survival" over two years of patients started on injectable gold as compared to Auranofin was similar with both drugs, but was only about 35%–40%. Cumulative "survival" for those patients on injectable gold was significantly less than for those on Auranofin because of toxicity. In the study by Bombardier and colleagues,[32] Auranofin therapy was shown not only to suppress clinical features of the disease as measured by standard variables, but also significantly improved a range of outcomes relevant to the patient's quality of life.

References

1. Lande K. Die Gunstige Beein Flussung Schleichender DaverinFekte durch Solganol. *Münch Med Wochenschr* 1927; 1132–4.

2. Forestier J. Rheumatoid arthritis and its treatment by gold salts. *Lancet* 1934; 2:646–8.

3. Fraser TN. Gold treatment in rheumatoid arthritis. *Ann Rheum Dis* 1945; 4:71–5.

4. The Research Sub-committee of the Empire Rheumatism Council. Gold therapy in rheumatoid arthritis: report of a multicentre controlled trial. *Ann Rheum Dis* 1960; 19:95–119.

5. The Research Sub-committee of the Empire Rheumatism Council. Gold therapy in rheumatoid arthritis: final report of a multicentre controlled trial. *Ann Rheum Dis* 1961; 20:315–54.

6. The Co-operating Clinics of the American Rheumatism Association. A controlled trial of gold salt therapy in rheumatoid arthritis. *Arthritis Rheum* 1973; 16:353–8.

7. Davis P. Auranofin. In: E.C. Huskisson, ed. *Clinics in rheumatic disease.* London: W.B. Saunders, 1984; 10:2, 369–84.

8. Gibson T, Huskisson EC, Wojtulewski JA, et al. Evidence that d-penicillamine alters the course of rheumatoid arthritis. *Rheumatol Rehab* 1976; 15:211–15.

9. Dwosh IL, Stein HB, Urowitz MB, et al. Azathioprine in early rheumatoid arthritis. *Arth Rheum* 1977; 20:685–92.

10. Currey HLF, Harris J, Mason RM, et al. Comparison of azathioprine, cyclophosphamide and gold in the treatment of rheumatoid arthritis. *Br Med J* 1974; 3:763–6.

11. Kean WF, Anastassiades TP. Long term chrysotherapy: incidence of toxicity and efficacy during sequential time periods. *Arth Rheum* 1979; 22:495–501.

12. Hever MA, Pietrusko RG, Morris RW, et al. An analysis of worldwide safety experience with Auranofin. *J Rheumatol* 1985; 12:695–9.

13. Penneys NS, Ackerman AB, Gottlieb NL. Gold dermatitis. *Arch Dermatol* 1974; 109:372–6.

14. Klinefelter HF. Reinstitution of gold therapy in rheumatoid arthritis after mucocutaneous reaction. *J Rheumatol*

References
1. Messerli, Franz H: The Age Factor in Hypertension. Hospital Practice, January 15, 1986, Vol. 21, No. 1, pp. 103-112.
2. Thananopavarn, C., et. al: Clonidine, A Centrally Acting Sympathetic Inhibitor, as Monotherapy for Mild to Moderate Hypertension. American Journal of Cardiology 1982, Vol. 49, pp. 153-158.
3. Catapres Product Monograph.
4. Sowers, James R.: Hypertension in the Elderly, Monograph 1986.
5. Guthrie, Gordon P. Jr.: Diabetes and Hypertension: Clonidine Monotherapy. Reprint from: Low Dose Oral and Transdermal Therapy of Hypertension by Steinkopff Verlagg Darmstadt, 1985.
6. Drayer, Jan I.M.: Weber, Michael A.: Current concepts in the Evaluation and Treatment of Patients with Mild to Moderate Hypertension. Hospital Formulary, Vol. 18, No. 2, pp. 164-170.
7. Tuck, Michael L.: Obesity and Hypertension. Monograph 1983.

1975; 2:21–7.

15. van Riel PL, Gribnau FW, van de Putte LB, et al. Loose stools during Auranofin treatment: clinical study and some pathogenetic possibilities. *J Rheumatol* 1983; 10:222–6.

16. Newton P, Swinburn WR, Swinson DR. Proteinuria with gold therapy: When should gold be permanently stopped? *Br J Rheumatol* 1983; 22:11–7.

17. Samuels B, Lee JC, Engleman EP, et al. Membranous nephropathy in patients with rheumatoid arthritis: relationship to gold therapy. *Medicine* 1978; 57:319–27.

18. Percy JS. Gold in the treatment of Felty's syndrome. *J Rheumatol* 1981; 8:878–9.

19. Edelman J, Davis P, Owen ET. Prevalence of eosinophilia during gold therapy for rheumatoid arthritis. *J Rheumatol* 1983; 10:121–3.

20. Harth M, Hickey JP, Coulter WK, et al. Gold induced thrombocytopenia. *J Rheumatol* 1978; 5:165–72.

21. Aaron S, Davis P, Percy JS. Neutropenia occurring during the course of chrysotherapy. *J Rheumatol* 1985; 12:897–9.

22. Kay AGL. Myelotoxicity of gold. *Br Med J* 1976; 1:1266–8.

23. Halla JT, Hardin JG, Linn JE. Postinjection non-vasomotor reactions during chrysotherapy. *Arth Rheum* 1977; 20:1188–91.

24. Gould PW, McCormack PL, Palmer DG. Pulmonary damage associated with sodium aurothiomalate therapy. *J Rheumatol* 1977; 4:252–60.

25. Favreau M, Tannenbaum H, Lough J. Hepatitic toxicity associated with gold therapy. *Ann Intern Med* 1977; 87:717–9.

26. Stein HB, Urowitz MB. Gold induced enterocolitis. *J Rheumatol* 1976; 2:21–6.

27. Sharp JT, Lidsky MD, Duffy J, et al. Comparison of two dosage schedules of gold salts in the treatment of rheumatoid arthritis: relationship of serum gold levels to therapeutic response. *Arth Rheum* 1977; 20:1179–87.

28. Biggs DF, Boland DN, Davis P, et al. In vitro binding and pharmacokinetics of gold salts to plasma proteins and chelating agents. *J Rheumatol* (suppl 5) 1979; 6:68–73.

29. Davis P, Menard H, Thompson J, et al. One year comparative study of gold sodium thiomalate and Auranofin in the treatment of rheumatoid arthritis. *J Rheumatol* 1985; 12:60–7.

30. Davis P. The cost of parenteral gold vs oral gold in the longterm treatment of rheumatoid arthritis. *J Rheumatol* 1986; 13:664.

31. Harth M, Davis P, Thompson J, et al. Comparison between sodium aurothiomalate and auranofin in rheumatoid arthritis: results of a two year open randomised study. *Scand J Rheumatol* 1987; 16:117–84.

32. Bombardier C, Ware J, Russell IJ, et al. Auranofin therapy and quality of life in patients with rheumatoid arthritis. *Am J Med* 1986; 81:565–78.